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denatured albumin, reticulated hemoglobin, and esters of polyglutamic and polyaspartic acids, said method comprising the step of forming the microballoons in the presence of [a] the gas mixture comprising a physiologically acceptable gas[, said physiologically acceptable gas being] selected from the group consisting of SF_6, CF_4, $CBrF_3$, C_4F_8, $CClF_3$, C_2F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$ and C_4F_{10}, said gas or at least a gas in said gas mixture being such that, under standard conditions, the pressure difference ΔP between pressures at which the bubble counts are about 75% and 25% of the original bubble count is at least 25Torr.

REMARKS

The Amendment accompanies a request for a continued prosecution application (CPA) under 37 C.F.R. §1.53(d) as requested by examiners Hollinden and Hartley during an interview with patentees' representatives Crawford, Rhoads and Chen on November 29, 2000; see paper no. 17. This Amendment, in effect, responds to the Official Action of August 29, 2000, a final rejection. The CPA filing insures consideration of this Amendment on the mertis.

Claims 1-7 and 13-48 are pending in this application. Each of the pending independent claims 1, 2, 13, 15-20, and 32-34 has been amended without prejudice to place them in better condition for allowance. Specifically, each of these independent claims has been amended to incorporate limitations found in the dependent claims, not for prior art reasons, but to more clearly define the stabilized microbubbles and microballoons claimed. For example, independent claims 1, 2, 13, 15, 18, and 32, which are directed to various methods of making stabilized microbubbles, have been amended to incorporate limitations found in dependent claims 4-5 or 23-24 that more clearly define the stabilized microbubbles claimed. The remaining independent claims 16, 17, 19, 20, 33, and 34, which are directed to various methods of making

microballoons, have been amended to incorporate limitations found in dependent claims 27-29 that more clearly define the microballoons claimed.

Other minor grammatical deletions or additions were made within these claims to make the language within the claims more consistent with each other.

Dependent claims 4-5, 23-24, and 27-29 have been cancelled. Additionally, dependent claims 6, 7, 25, and 26 have been amended to properly depend from an existing claim.

In making these amendments, no new matter was added and no broadening of the original claims was done.

Applicants believe that these claims are patentable for the same reasons that the original claims were patentable as explained in Applicants' March 29, 2000 Amendment And Response To Office Action. They are supported in the specification as shown in Applicants' Preliminary Amendment filed July 15, 1998. Applicants are not aware of any prior art that has all of the elements of the claims or which in proper combination with other prior art would provide all of the elements of the claims. For the Examiner's convenience, Applicants briefly summarize below the references emphasized by the Examiner in the Final Office Action dated August 29, 2000 and how these new claims, like the previous ones, are new and nonobvious in view of those references:

A. Albayrak (U.S. Patent No. 5,730,954)

Albayrak discloses crystalline cavitate or clathrate forming host/guest complexes which dissolve to release free gas microbubbles. Albayrak also discloses the use of undenatured albumin and phosphatidylcholine in the liquid vehicle as viscosity or thickening agents which do not stabilize, surround, or form any kind of layer around the free gas microbubble.

B. Rossling (U.S. Patent No. 5,501,863)

Rossling discloses rigid particulate microparticles formed from aldehydes which may be porous and are often crystalline. Rossling also discloses the use of undenatured albumin as a coupling agent to attach to the surface of the aldehydes used to make the microparticles.

C. Tickner I (U.S. Patent No. 4,265,251)

Tickner I discloses free gas microbubbles dispersed in gelatin membranes, which are warmed and dissolved in order to release free gas microbubbles. The gelatin acts as a viscosity barrier to reduce coalescence of the free gas microbubbles.

D. Tickner II (U.S. Patent No. 4,276,885)

Tickner II discloses saccharide microparticle precursors which dissolve in the bloodstream to release free gas microbubbles. These saccharide microparticles are porous, crystalline, rigid, and preferably ground.

E. Glajch (U.S. Patent No. 5,147,631)

Glajch discloses microparticles made of inorganic material. These microparticles are porous and may be crystalline.

F. Hilmann (U.S. Patent No. 4,466,442)

Hilmann discloses a solution containing a selected amount of tenside, viscosity raising compound and gas.

G. Lincoff I, Lincoff II, Gardner, Jacobs (collectively, the Ocular Documents)

Each of these Ocular Documents are directed to the use of a single large fluorinated gas bubble as intraocular tamponades for the treatment of retinal tears or detachments in the eye. Specifically, these Ocular Documents discuss the desirability of free gas expansion within the eye - a property which teaches away from the use of fluorinated gas as ultrasound contrast agents

since gas expansion in the bloodstream could lead to serious health effects (i.e., embolism) in the patient.

H. Applicant's Stabilized Microbubbles And Microballoons

Albayrak, Rossling, Tickner I, Tickner II, Glajch, Hilmann, and the Ocular Documents do not, individually or in combination, teach, suggest, or disclose the Applicants' stabilized microbubbles wherein a fluorinated gas or gas mixture is bounded by a stabilizing layer of one or more film forming phospholipids in lamellar or laminar form at the gas/liquid interface. The method of making Applicants' stabilized microbubbles are claimed in claims 1-3, 6, 7, 13-15, 18, 21, 25, 26, 32, 35, 37, 38-42.

Albayrak, Rossling, Tickner I, Tickner II, Glajch, Hilmann, and the Ocular Documents also do not, individually or in combination, teach, suggest, or disclose the Applicants' microballoons wherein a fluorinated gas or gas mixture is bounded by an organic polymer envelope at the gas/liquid interface, said envelope formed from one or more polymers selected from the group consisting of polylactic or polyglycolic acid and their copolymers, denatured albumin (see Example 1 in the specification), reticulated hemoglobin, and esters of polyglutamic and polyaspartic acids. The method of making Applicants' microballoons are claimed in claims 16, 17, 19, 20, 22, 30, 31, 33, 34, 36, 43-48.

Additionally, Albayrak, Rossling, Tickner I, Tickner II, Glajch, Hilmann, and the Ocular Documents also do not, individually or in combination, teach, suggest, or disclose forming the Applicants' stabilized microbubbles or microballoons by the gas substitution method of claims 2, 3, and 18-22.

Thus, as these pending claims 1-3, 7-22, 26, and 30-48 are fully supported in the specification and are fully patentable over any references cited, favorable action on these claims is requested.

If there are any questions, the Examiner is respectfully asked to contact the undersigned.

Respectfully submitted,

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